Remarks

Claims 1-8 and 22 were pending. Applicants have canceled claims 3 and 6-7 without prejudice to Applicants' right to pursue their subject matter in the present application and in related applications. Applicants have amended claims 1-2, and 22.

Applicants have amended claim 1 for grammatical consistency, to delete unnecessary words, and to recite comparing the expression level in the mammal of interest with a reference. Support for the amendments to claim 1 is found in the original application at least, for example, in paragraphs [0014] and [0064] and original claim 1.

Applicants have amended claim 2 to recite that the at least one control sample is a kidney sample and to recite that the at least one control mammal is of the same species as the mammal of interest. Support for the amendments to claim 2 is found in the original application at least, for example, in paragraph [0058].

Applicants have amended claim 22 to delete unnecessary words and for consistency with the claim from which it depends.

Applicants submit that the present amendment introduces no new matter into the application.

As this amendment cancels some rejected claims and amends others, presenting them in better form for consideration on appeal, Applicants request admission of this amendment under 37 C.F.R. § 1.116(b).

Accordingly, claims 1-2, 5, 8 and 22 are pending and presented for examination.

35 U.S.C. § 112, second paragraph

The Office action rejected claim 3 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have canceled claim 3 without prejudice and request withdrawal of the rejection.

35 U.S.C. § 112, enablement

The Office action rejected claims 1-3, 5-8, and 22 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Office action acknowledged that the specification enables a method of diagnosing lupus nephritis (LN) in a mouse wherein the method comprises obtaining a kidney sample from a control mouse and a mouse with LN; determining the mRNA transcript level of midkine; comparing mRNA transcript level of midkine between a control and mouse with LN, wherein an increase in midkine mRNA transcript level, relative to the control, indicates that said mouse has an increased likelihood of LN. The action nevertheless disputed whether the application enables methods to diagnose systemic lupus erythematosus (SLE) or LN in mouse or human by detecting elevated midkine expression. The Office action alleged that the specification does not enable a person skilled in the art to make and use the invention commensurate with the scope of the claims.

Applicants request reconsideration and withdrawal of the rejection in view of the amendments to the claims.

As amended, claim 1 recites a method of diagnosing lupus nephritis in a mammal of interest selected from the group consisting of a human and a mouse, the method comprising the steps of: (a) detecting an expression level of midkine gene in a kidney sample isolated from the mammal of interest, wherein the mammal of interest is selected from the group consisting of a human and a mouse; and (b) comparing the expression level in the mammal of interest with a reference, wherein an elevated expression level in the mammal of interest as compared to the reference indicates that the mammal of interest has an increased likelihood of lupus nephritis.

Biological samples

The Office action acknowledged that the specification teaches detection of LN by elevated midkine expression levels in mouse kidney samples. The Office action alleged, however, that the diagnosis of LN by elevated expression in a urine sample or a blood sample would be unpredictable and would require undue experimentation. To address this concern, Applicants have amended claim 1 delete the references to urine samples and blood samples.

Likewise, Applicants have canceled claim 6 without prejudice, which was drawn to any tissue sample.

At least one control mammal

The Office action alleged that the control mammal of claim 2 can be broadly drawn to any animal, and that it would be unpredictable that any mammal could be used as a control to determine elevated expression levels in mouse or human. Applicants have amended claim 2 to recite that the control mammal is of the same species as the mammal of interest.

As compared to a reference

The Office action acknowledged that the specification enables diagnosing LN using a comparison between midkine transcript levels in a control and a mouse. The Office action alleged, however, that claim 1 is drawn to detecting an elevated expression level without comparing it to any control, and that it is unpredictable that any elevated expression will diagnose LN. Applicants have amended the claims to recite a comparison between expression levels in a mammal of interest with a reference, wherein an elevated expression level in the mammal of interest as compared to the reference indicates that the mammal of interest has an increased likelihood of lupus nephritis.

Mouse and human

The Office action alleged that the skilled artisan would have to examine midkine expression in any biological samples in any mammal in order to diagnose LN. As noted above, Applicants have addressed the concern regarding "any biological sample" by amending claim 1 to recite detection of midkine expression in a kidney sample. Moreover, Applicants have addressed the concerns regarding "any mammal" by amending claim 1 to recite mouse or human, and by amending claim 2 to recite a control sample which is of the same species as the mammal

of interest. The Office action stated that claim 6 is not limited to mouse and human. As noted above, Applicants have canceled claim 6 without prejudice.

Applicants have discovered, using a mouse model accepted in the art, that midkine expression levels are indicative of a likelihood of lupus, enabling diagnostic methods as claimed in amended claim 1. These methods are novel and inventive, as indicated by the withdrawal of all rejections under 35 U.S.C. §§ 102 and 103.

In amended claim 1, Applicants have claimed a method of diagnosing lupus nephritis in a mammal of interest selected from the group consisting of a human and a mouse. Thus, the claims are narrowly drawn to the use of midkine expression levels from a mouse (the species in which the experiments were performed) or a human (the species for which the model species serves as a model).

The Office action acknowledges that the specification is enabling with respect to diagnosis of lupus in mice.

Applicants submit that, with respect to the amended claims, the only issue is whether the methods enabled by the instant application bear any reasonable correlation with the scope of the claims. If they do, the rejection should be withdrawn.

Animal models are accepted by those of ordinary skill in the art as a means to generate data relevant to human biology. Data from animal models are accepted as a proxy for data in humans by the FDA as a precursor to human clinical trials. Similarly, the USPTO accepts data from animal models and does not routinely require human clinical trials before allowing claims encompassing diagnosis or treatment of humans. In the context of the utility requirement, for example, "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." MPEP § 2107.03(IV).

Here, although the issue is one of the scope of enablement, the USPTO's position remains the same. According to MPEP § 2164.02, if one skilled in the art accepts an animal model as reasonably correlating to a specific human condition, the animal model example is, in effect, a "working example." A rigorous or an invariable exact correlation is not required.

Thus, if one skilled in the art accepts the mouse model for lupus as a model for human lupus, the enabled working example of diagnosis in the mouse model is also deemed an enabled working example of diagnosis in humans for purposes of 35 U.S.C. § 112. Although the Office action argues that animal models have limitations, the Office action itself and the art cited therein repeatedly acknowledge that the animal models are indeed models for lupus and are useful in that regard. It bears repeating that, under Federal Circuit law and MPEP § 2164.02, a rigorous or an invariable exact correlation is not required.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Mouse and human—further remarks by Applicants

Applicants also wish to note their disagreement with the following (nonexhaustive list of) points in the Office action:

Applicants disagree with the allegation on page 13 that "the skilled artisan would need to determine if any variant of any fragment of the midkine gene would have the same level of expression in both mouse and human so as to be diagnostic for lupus." The practice of the invention does not require that mouse and human expression "have the same level of expression." All that is required is that elevated expression be indicative of an increased likelihood of lupus. An elevated level of expression would be determined by comparison to a reference such as, for example, an expression level of a normal tissue from the same species, an expression level of a diseased tissue from the same species, or a threshold distinguishing the two.

Applicants disagree with the allegation on pages 13 and 14 that the "skilled artisan would need to determine the necessary amino acids needed to define the midkine gene in both animals and determine if changes in the amino acids would have the same change in functionality in both animals." The midkine genes in mouse and human are known and well characterized and were

well characterized at the time of the invention.[1] Furthermore, the invention does not relate to changes in midkine functionality, but to the use of midkine expression levels as a diagnostic.

Applicants disagree with the allegation on page 14 that "the skilled artisan would also have to determine if population stratification would affect expression levels of the midkine gene in human." "Population stratification" relates to a confounding factor in genetic association studies. The claims do not require or involve genetic association studies in humans, but merely the use of midkine expression levels as a diagnostic.

At page 14, the Office action argues at length that Kotzin *et al.* teaches that lupus is complex; that many factors complicate the genetic analysis of lupus; that different combinations of genes can cause the lupus phenotype; that animal models provide an opportunity to control environmental exposures; that initial genetic mapping in a complex trait can give misleading findings, and that a human gene may not be in a region syntenic to a murine locus. The present invention, however, does not involve a genetic linkage analysis of the type discussed in Kotzin *et al.* Rather, the invention relates to midkine expression levels, which Applicants have discovered to be indicative of a likelihood of lupus.

At page 15, the Office action alleges that expression of genes is affected by surrounding genes and argues that it is "unclear if the expression of midkine gene would be the same in mouse and human because it is not clear from the specification that the midkine gene is in a similar region in a human as a mouse." Applicants do not believe that gene expression is primarily a function of surrounding genes. To the extent that the rejection relies on the human midkine gene not being in a "similar region" and that the location of the human midkine gene affects its expression, Applicants request that corresponding evidence be introduced so that Applicants can respond accordingly.

Applicants again request that the enablement rejection be reconsidered and withdrawn.

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[1] Applicants note, for example, that Tsutsui *et al.* (1991) discloses the nucleic acid and amino acid sequences of human midkine. Tsutsui *et al.* (1991) Biochem. Biophys. Res. Comm. 176(2):792-97, pages 795-76. Moreover, Tsutsui *et al.* (1991) teaches (at pages 795-96) an alignment of human and mouse midkine protein which specifically shows the conserved regions between mouse and human and, therefore, shows regions and amino acids which may be relevant to midkine function.

Conclusion

Examiner Salmon is invited to telephone the undersigned attorney to discuss any remaining issues.

Respectfully submitted,

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